Policy Statement

Locoregional Ablation
Laser ablation for the treatment of patients with primary or metastatic hepatic lesions is considered investigational.

Microwave ablation may be considered medically necessary for the treatment of patients with hepatic lesions for any of the following conditions:

- **Primary hepatocellular carcinoma (HCC)** when the all of the following criteria are met:
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Presence of three or fewer hepatic lesions
  - Each lesion measures five centimeters (cm) or less in diameter using current technology
  - Absence of extrahepatic metastatic disease
  - All tumor foci can be adequately treated (complete ablation is determined by preoperative imaging)

- **Primary HCC, as a bridge to transplantation**, when all of the following criteria are met:
  - Intent is to prevent further tumor growth and to maintain a patient's candidacy for liver transplant
  - Presence of three or fewer hepatic lesions
  - Each lesion measures five centimeters (cm) or less in diameter using current technology
  - No evidence of extrahepatic spread and/or macrovascular involvement (i.e., portal or hepatic veins)

  **Note:** Criteria for ablative therapies as a bridge to transplantation are generally consistent with the United Network for Organ Sharing (UNOS) policy on Organ Distribution: Liver Transplant Candidates with Hepatocellular Carcinoma (HCC); Section 3.6.4.4 (11/9/2010).

- **Hepatic metastases from colorectal cancer** when all of the following criteria are met:
  - Presence of four to five or fewer hepatic lesions
  - Each lesion measures five centimeters (cm) or less in diameter using current technology
  - Absence of extrahepatic metastatic disease
  - All tumor foci can be adequately treated (complete ablation is determined by preoperative imaging)

- **Hepatic metastases from neuroendocrine tumors** when all of the following criteria are met:
  - Patient has symptomatic disease (e.g., wheezing, flushing of the skin, abdominal cramps, diarrhea, heart disease)
  - Systemic therapy has failed to control symptoms (e.g., Octreotide therapy)
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
Absence of extrahepatic metastatic disease
• Each lesion measures five centimeters (cm) or less in diameter using current technology

Microwave ablation for primary HCC or hepatic metastases is considered investigational for the treatment of any of the following:

• Primary HCC when there are either of the following:
  • More than three hepatic lesions nodules
  • When not all sites of tumor foci can be adequately treated
• Primary HCC when used to downstage (downsize) HCC in patients being considered for liver transplant
• Hepatic metastasis from colorectal cancer or neuroendocrine tumors not meeting the medically necessary criteria above
• Hepatic metastases from other types of cancer with the exception of colorectal or neuroendocrine cancer tumors

**Policy Guidelines**

Downstaging (downsizing) therapy is used to reduce the tumor burden in selected patients with more advanced HCC (without distant metastasis) that are beyond the accepted transplant criteria.

**Neuroendocrine Tumors**

Neuroendocrine tumors (NETs) may be referred to by their anatomical location (e.g., pulmonary neuroendocrine tumor, gastroenteropancreatic neuroendocrine tumor). Neuroendocrine tumors include the following:

• Carcinoid tumors
• Islet cell tumors (or pancreatic endocrine tumors)
• Neuroendocrine unknown primary
• Adrenal gland tumors
• Pheochromocytoma/paraganglioma
• Poorly differentiated (high grade or anaplastic)/small cell
• Multiple endocrine neoplasia, Type 1 (also known as MEN-1 syndrome or Wermer's syndrome)
• Multiple endocrine neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

Symptomatic disease from neuroendocrine tumors may include hot, red flushing of the face, severe and debilitating diarrhea, asthma attacks, palpitations, low blood pressure, fatigue, dizziness, and weakness. Extreme symptoms may include heart disease, bronchial constriction, and bowel obstruction.

Systemic therapies for neuroendocrine tumors vary depending on the location and characteristics. Therapies may include, but are not limited to: octreotide, interferon, cytotoxic chemotherapy, angiogenesis inhibitors, and epidermal growth factor inhibitors.

**Coding**

There are no CPT codes specific to microwave ablation. The following CPT code would likely be used:

- **32998**: Ablation therapy for reduction or eradication of one or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, radiofrequency, unilateral
- **47370**: Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
- **47380**: Ablation, open, of one or more liver tumor(s); radiofrequency
- **47382**: Ablation, one or more liver tumor(s), percutaneous, radiofrequency
- **47383**: Ablation, one or more liver tumor(s), percutaneous, cryoablation
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- **50592**: Ablation, one or more renal tumor(s), percutaneous, unilateral, radiofrequency

**Note**: According to an American Medical Association (AMA) publication (Clinical Examples in Radiology, Vol. 8, Issue 3; Summer 2012), “microwave is part of the radiofrequency spectrum, and simply uses a different part of the radiofrequency spectrum to develop heat energy to destroy abnormal tissue.” Therefore, AMA recommends that microwave ablation be reported using CPT codes for radiofrequency ablation – 32998 (pulmonary), 47382 (liver), and 50592 (renal).

If there is no specific CPT code for ablation, the unlisted CPT code for the anatomic area should be reported, such as code 60699 for unlisted procedure, endocrine system (for adrenal or thyroid ablation).

CPT code 76940 would be used to describe the ultrasound guidance for, and monitoring of, parenchymal tissue ablation.

There is a CPT category III code specific to focused ultrasound destruction of a breast tumor:
- **0301T**: Destruction/reduction of malignant breast tumor with externally applied focused microwave, including interstitial placement of disposable catheter with combined temperature monitoring probe and microwave focusing sensocatheter under ultrasound thermotherapy guidance

**Description**

Microwave ablation (MWA) is a technique to destroy tumors and soft tissue using microwave energy to create thermal coagulation and localized tissue necrosis. MWA is used to treat tumors not amenable to resection or to treat patients’ ineligible for surgery due to age, comorbidities, or poor general health. MWA may be performed as an open procedure, laparoscopically, percutaneously, or thoracoscopically under image guidance (e.g., ultrasound, computed tomography, magnetic resonance imaging) with sedation, or local or general anesthesia. This technique is also referred to as microwave coagulation therapy.

**Related Policies**

- Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors
- Cryosurgical Ablation of Primary or Metastatic Liver Tumors
- Radioembolization for Primary and Metastatic Tumors of the Liver
- Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
- Radiofrequency Ablation of Primary of Metastatic Liver Tumors
- Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Regulatory Status

Several devices have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for microwave ablation (MWA). Covidien’s (now Medtronic’s) Evident™ Microwave Ablation System was cleared for marketing through the 510(k) process for soft tissue ablation, including partial or complete ablation of nonresectable liver tumors. The following devices have 510(k) clearance for MWA of (unspecified) soft tissue:

- BSD Medical’s (now Persoon) MicroThermX® Microwave Ablation System (MTX-180)
- Valleylab’s (subsidiary of Covidien) VivaWave® Microwave Ablation System
- Vivant’s (acquired by Valleylab in 2005) Tri-Loop™ Microwave Ablation Probe
- MicroSurgeon’s Microwave Soft Tissue Ablation System
- MicroSulis Medical’s (now part of AngioDynamics) Acculis® Accu2i
- NeuWave Medical’s Certus® 140

The FDA determined that these devices were substantially equivalent to existing radiofrequency and MWA devices. FDA product code: NEY.

This evidence review does not address MWA for the treatment of splenomegaly or ulcers or as a surgical coagulation tool.

Rationale

Background

Microwave Ablation

Microwave ablation (MWA) is a technique that uses microwave energy to induce an ultra-high speed, 915 MHz or 2.450 MHz (2.45 GHz), alternating electric field, which causes water molecule rotation and creates heat. This results in thermal coagulation and localized tissue necrosis. In MWA, a single microwave antenna or multiple antennas connected to a generator are inserted directly into the tumor or tissue to be ablated; energy from the antennas generates friction and heat. The local heat coagulates the tissue adjacent to the probe, resulting in a small, 2- to 3-cm elliptical area (5 × 3 cm) of tissue ablation. In tumors greater than 2 cm in diameter, 2 to 3 antennas may be used simultaneously to increase the targeted area of MWA and shorten operative time. Multiple antennas may also be used simultaneously to ablate multiple tumors. Tissue ablation occurs quickly, within 1 minute after a pulse of energy, and multiple pulses may be delivered within a treatment session, depending on tumor size. The cells killed by MWA are typically not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the margins. Treatment may be repeated as needed. MWA may be used for the following purposes: (1) to control local tumor growth and prevent recurrence; (2) to palliate symptoms; and (3) to extend survival duration.

MWA is similar to radiofrequency (RFA) and cryosurgical ablation. However, MWA has potential advantages over RFA and cryosurgical ablation. In MWA, the heating process is active, which produces higher temperatures than the passive heating of RFA and should allow for more complete thermal ablation in less time. The higher temperatures reached with MWA (>100°C) can overcome the “heat sink” effect in which tissue cooling occurs from nearby blood flow in large vessels, potentially resulting in incomplete tumor ablation. MWA does not rely on the conduction of electricity for heating and, therefore, does not flow electrical current through patients and does not require grounding pads, because there is no risk of skin burns. Additionally, MWA does not produce electric noise, which allows ultrasound guidance during the procedure without interference, unlike RFA. Finally, MWA can take less time than RFA, because multiple antennas can be used simultaneously.

Adverse Events

Complications from MWA are usually mild and may include pain and fever. Other complications associated with MWA include those caused by heat damage to normal tissue adjacent to the
tumor (e.g., intestinal damage during MWA of the kidney or liver), structural damage along the probe track (e.g., pneumothorax as a consequence of procedures on the lung), liver enzyme elevation, liver abscess, ascites, pleural effusion, diaphragm injury, or secondary tumors if cells seed during probe removal. MWA should be avoided in pregnant women because potential risks to the patient and/or fetus have not been established, and in patients with implanted electronic devices (e.g., implantable pacemakers) that may be adversely affected by microwave power output.

Applications
MWA was first used percutaneously in 1986 as an adjunct to liver biopsy. Since then, MWA has been used to ablate tumors and tissue to treat many conditions including hepatocellular carcinoma, breast cancer, colorectal cancer metastatic to the liver, renal cell carcinoma, renal hamartoma, adrenal malignant carcinoma, non-small-cell lung cancer, intrahepatic primary cholangiocarcinoma, secondary splenomegaly and hypersplenism, abdominal tumors, and other tumors not amenable to resection. Well-established local or systemic treatment alternatives are available for each of these malignancies. The potential advantages of MWA for these cancers include improved local control and other advantages common to any minimally invasive procedure (e.g., preserving normal organ tissue, decreasing morbidity, shortening length of hospitalization). MWA also has been investigated as a treatment for unresectable hepatic tumors, as both primary and palliative treatment, and as a bridge to liver transplant. In the latter setting, MWA is being assessed to determine whether it can reduce the incidence of tumor progression while awaiting transplantation and thus maintain a patient’s candidacy while awaiting liver transplant.

Hepatic Tumors
Hepatic tumors can arise either as primary liver cancer (HCC) or by metastasis to the liver from other primary cancer sites. Local therapy for hepatic metastasis may be indicated when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies. At present, surgical resection with adequate margins or liver transplantation constitutes the only treatments available with demonstrated curative potential. Partial liver resection, hepatectomy, is considered the criterion standard. However, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve.

Various locoregional therapies for unresectable liver tumors have been investigated including: microwave coagulation, RFA, cryosurgical ablation (cryosurgery), laser ablation, transhepatic artery embolization/chemoembolization (TACE), percutaneous ethanol injection, and radioembolization (Yttrium-90 microspheres).

Literature Review
Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition. The findings of the literature review are summarized next with select studies.

Breast Cancer
A 2010 systematic review of ablation techniques by Zhao et al for breast cancer found that only 0% to 8% of breast cancer tumors were completely ablated with microwave ablation (MWA).1 The studies identified by reviewers were mostly feasibility and pilot studies conducted in research settings.
In 2012, Zhou et al reported on 41 patients treated with MWA directly followed by mastectomy for single breast tumors with a mean volume of 5.26 cm (range, 0.09-14.14 cm).² Complete tumor ablation was found by microscopic evaluation in 37 (90%) of the 41 tumors ablated (95% confidence interval [CI], 76.9% to 97.3%). Reversible thermal injuries to the skin and pectoralis major muscle occurred in 3 patients.

**Hepatocellular Carcinoma**

**Systematic Reviews**
Chinnaratha et al (2016) published a systematic review of RCTs and observational studies that compared the effectiveness and safety of radiofrequency ablation (RFA) with MWA in patients with primary hepatocellular carcinoma (HCC).³ MEDLINE, EMBASE, and Cochrane Central databases were searched between 1980 and 2014 for human studies comparing the 2 technologies. The primary outcome was the risk of local tumor progression (LTP); secondary outcomes were complete ablation, overall survival (OS), and major adverse events. Odds ratios (ORs) were combined across studies using a random-effects model. Ten studies (2 prospective, 8 retrospective) were included. The overall LTP rate was 14% (176/1298). There was no difference in LTP rates between RFA and MWA (OR=1.01; 95% CI, 0.67 to 1.50; p=0.9). The complete ablation rate, 1- and 3-year OS, and major adverse events were similar between the 2 modalities (p>0.05 for all). Subgroup analysis showed LTP rates were lower with MWA for treatment of larger tumors (OR=1.88; 95% CI, 1.10 to 3.23; p=0.02). No significant publication bias was detected nor was interstudy heterogeneity (I²<50%, p>0.1) observed for any measured outcomes.

Bertot et al (2011) conducted a systematic review of ablation techniques for primary and secondary liver tumors.⁴ Reviewers selected 2 studies⁵,⁶ (see Case Series section) using MWA (total N=1185 patients). Pooled analysis was performed using a random-effects model because of significant study heterogeneity. The pooled mortality rate for MWA was 0.23% (95% CI, 0.0% to 0.58%). The pooled rate of major complications following MWA was 4.6%.

In 2009, Ong et al conducted a systematic review of studies on MWA for primary and secondary liver tumors.⁷ Results pooled from 25 clinical studies suggested MWA is an effective and safe technique for liver tumor ablation and has low complication rates and OS rates comparable to hepatic resection. However, rates of local recurrence after MWA were higher than hepatic resection. In most studies, mean HCC recurrence rates were approximately 10% but were as high as 50% in some studies. OS rates for HCC were as high as 92% at 3 years and 72% at 5 years, comparable to OS rates for RFA and percutaneous ethanol injections. Pain and fever were the most frequently reported complications, which increased with more tumors, larger tumors, and number of microwave antennas used.

**Comparative Studies**
No RCTs comparing MWA with RFA were identified. The available studies are nonrandomized comparisons, and all except 1 study is retrospective.

Abdelaziz et al (2015) reported on a prospective study that evaluated the efficacy and safety of MWA and transarterial chemoembolization (TACE) for large tumors (5-7 cm) and assessed their effects on LTP and survival.⁸ Sixty-four patients with large lesions were divided into 2 groups treated by MWA or by TACE. Both groups were comparable in demographic and ultrasonographic tumor features. MWA completely ablated 75% of cases in fewer sessions than TACE, with a lower incidence of tumor recurrence (p=0.02), development of de novo lesions (p=0.03), and occurrence of posttreatment ascites (p=0.003). MWA also had higher OS rates (p=0.04) than TACE. Mean OS in the MWA group was 22 months and 14 months in the TACE group. Actuarial probabilities of survival at 12 and 18 months were 78% and 68%, respectively, in the MWA group and 52% and 29%, respectively, in the TACE group.

Vogl et al published a retrospective comparative study in 2015.⁹ It enrolled 53 patients with 68 liver lesions due to HCC. MWA was performed in 36 patients and RFA in 32 patients. There were no differences between groups on complete response immediately following treatment or for
progression-free survival at 12 months or OS at 3 years. In 2013, Ding et al retrospectively compared 113 patients treated with MWA for 131 HCC tumors and 85 patients treated with RFA for 98 HCC tumors. Rates of complete ablation, local recurrence, disease-free survival (DFS) and cumulative survival (at 1, 2, 3, and 4 years), and major complications did not differ significantly between groups.

In another 2013 study by Ding et al, complications were retrospectively compared between 556 patients treated with MWA for 1090 tumors (491 HCC, 18 cholangiocarcinoma, 47 liver metastases) and 323 patients treated with RFA for 562 liver tumors (279 HCC, 6 cholangiocarcinoma, 38 liver metastases). Rates of death (2/556 MWA, 1/323 RFA patients), as well as major and minor complications, did not differ significantly between groups.

In 2013, Takami et al reported on 719 patients treated with MWA for HCC (mean tumor size, 2.7 cm) at a single institution. OS rates were 97.7% at 1 year, 62.1% at 5 years, and 34.1% at 10 years. For 390 patients with 3 or fewer tumors measuring 3 cm or less, OS rates were 97.9% at 1 year, 70.0% at 5 years, and 43.0% at 10 years. When MWA results were compared with 34 patients treated at the same institution with hepatic resection, OS, DFS, and local recurrence rates did not differ significantly.

In a 2012 report on needle track seeding, Yu et al followed 1462 patients treated with MWA for 2530 liver tumors over a 14-year period. Twelve seeding nodules with a mean size of 2.3 cm (range, 1.3-3.9 cm) were found in 11 patients within 6 to 37 months (median, 10 months) after receiving MWA.

In 2011, Simo et al retrospectively compared MWA (13 patients with 15 HCC tumors) with RFA (22 patients with 27 HCC tumors) performed by a single surgeon. No significant differences were identified between treatment group characteristics, except for sex (54% vs 86% male, respectively). Average tumor size was 2.31 cm in the MWA group and 2.53 cm in the RFA group. Average tumor ablation volumes did not differ significantly for MWA (28.99 cm) and RFA (23.43 cm). In the MWA group, at a mean 7-month follow-up, the DFS rate was 54%, with 2 patients having received liver transplants, 31% having disease progression and 15% deceased. Mean follow-up in the RFA group was 19 months. This group experienced 50% OS: 4% of patients had liver transplants, 9% had disease progression, and 36% died. Operative times were shorter in the MWA group (112 minutes vs 149 minutes).

Case Series
In 2011, Zhou et al prospectively evaluated MWA in 215 patients with HCC tumors of 6 cm or less (median size, 2.9 cm) in a single-center, phase 2 study. Technical effectiveness was reported in all patients. OS rates at 1, 2, 3, 4, and 5 years were 94%, 82.9%, 66%, 54.1%, and 44.4%, respectively, and median OS time was 40 months (range, 4-106 months). Complications related to the procedure included 3 cases of pleural effusion and 1 case of bile duct injury.

In another prospective study by Zhou et al (2009), MWA was performed on 124 patients with 144 HCC lesions and 28 patients with 35 hepatic metastases. Included in the 152 subjects were 59 patients with 61 lesions (mean size, 2.7 cm) located less than 0.5 cm from the gastrointestinal (GI) tract and 93 patients with 126 lesions (mean size, 2.4 cm) located more than 0.5 cm from the GI tract. For lesions less than 0.5 cm from the GI tract, margin temperatures were monitored during ablation and, to prevent thermal injury, ethanol injections were placed into marginal tumor tissue in 33 lesions that protruded or were in contact with the GI tract. No procedural complications were noted, though tumor seeding occurred in 3 patients. Complete ablation was achieved in 47 (88.7%) of 53 lesions in the group with tumors near the GI tract and 116 (92.1%) of the other 126 lesions, as confirmed by imaging during the 3- to 32-month follow-up. LTP occurred in 16 tumors by 9 months. Separate treatment outcomes for HCC tumors and hepatic metastasis were not provided.
In 2009, Liang et al retrospectively reviewed complications experienced with MWA for the treatment of 1928 malignant liver tumors in 1136 patients at a single institution. Each patient received an average of 1.8 treatment sessions (total treatment sessions, 3697). Thirty (2.6%) patients experienced major complications, which included 5 cases of liver abscess and empyema, 2 bile duct injuries, 2 colon perforations, 5 tumor seedings, 12 pleural effusions requiring thoracentesis, 1 hemorrhage requiring arterial embolization, and 3 skin burns requiring. Two deaths occurred within 14 days of MWA in patients with Child-Pugh class B uncompensated cirrhosis. One patient (age 78 years) had multiorgan failure and another (age 83 years) had respiratory and cardiac failure. Minor more frequent complications included fever (83.4%), pain (80.1%), asymptomatic pleural effusion (10.4%), and thickening of the gallbladder wall (2.8%), and arterioportal shunt (0.3%), small stricture of the bile duct (0.4%), and skin burn requiring no treatment (1.6). A significantly higher rate of major complications and more ablation sessions were experienced when a non-cooled-shaft antenna was used during the period of 1994 to 2005 (n=583) than with newer technology; cooled-shaft antennas were used beginning in 2005 (n=583).

Taniai et al (2006) reported on 30 patients with multiple HCC tumors who underwent reduction hepatectomy with postoperative TACE. Before surgery, patients were randomized to no intraoperative adjuvant therapy (n=15) or intraoperative adjuvant therapy with either MWA (n=10) or RFA (n=5) of satellite lesions. No significant differences were identified between the no intraoperative adjuvant therapy and intraoperative adjuvant therapy groups, including sex, age, nodule size (maximum tumor size, 4.3 cm vs 3.8 cm, respectively), Child-Pugh cirrhosis class, and number of nodules. Cumulative survival rates at 3 and 5 years did not differ significantly between the no intraoperative adjuvant therapy group (35.0% and 0%, respectively) and the intraoperative adjuvant therapy group (35.7% and 7.7%, respectively). The α-fetoprotein level, number of tumors, maximum tumor size, and clinical stage, but not intraoperative adjuvant therapy, were identified as independent prognostic survival factors.

Lu et al (2005) reported on a retrospective comparison of 102 patients with HCC treated with MWA (49 patients with 98 nodules; mean size, 2.5 cm) or RFA (53 patients with 72 nodules; mean size, 2.6 cm). Patient follow-up was about 25 months in both groups. Complete ablation did not differ significantly between groups (95% [93/98] tumors in the MWA group vs 93% [67/72] tumors in the RFA group). However, complete ablation rates improved for smaller tumors of less than 3 cm in size to 98.6% (73/74) in the MWA group and 98% (50/51) in the RFA group. In tumors larger than 3 cm, complete ablation rates declined to 83.3% (20/24) in the MWA group and 81% (17/21) in the RFA group. There were also no significant differences between groups in rates of local tumor recurrence (11.8% for MWA vs 20.9% for RFA), major complications (8.2% vs 5.7%, respectively), or DFS at 1, 2, and 3 years (45.9%, 26.9%, and 26.9% vs 37.2%, 20.7%, and 15.5%, respectively).

In 2002, Shibata et al reported on 72 consecutive patients with 94 small HCC nodules randomized by sealed envelope to MWA or RFA performed by a single surgeon. No significant differences were identified between treatment group characteristics (e.g., sex, age, nodule size, Child-Pugh class, number of nodules). In the RFA group, complete ablation was seen in 46 (96%) of 48 nodules (mean size, 2.3 cm; range, 1.0-3.7 cm) and 41 (89%) of 46 nodules (mean size, 2.2 cm; range, 0.9-3.4 cm) treated with MWA (p=0.26). Treatment outcomes did not differ significantly between groups in rates of untreated disease during the 6- to 27-month follow-up (8/46 nodules for MWA vs 4/48 nodules for RFA), or major complication rates (4 vs 1, respectively). Major complications included 1 case of segmental hepatic infarction in the RFA group compared with 1 case of each of the following in the MWA group: liver abscess, cholangitis with intrahepatic bile duct dilatation, subcutaneous abscess with skin burn, and subcapsular hematoma. Life-threatening complications were not reported. The number of treatment sessions required per nodule in the RFA group (1.1) was significantly lower than in the percutaneous MWA group (2.4; p<0.001). However, treatment time per session was significantly shorter with MWA (33 minutes) than with RFA (53 minutes).
Hepatic Metastases from Primary Cancers from Other Sites
Systematic Reviews

A 2014 Health Technology Assessment\(^1\) and a 2013 Cochrane review\(^2\) reported on ablation for liver metastasis. Reviewers found insufficient evidence to determine any benefits of MWA for liver metastasis over surgical resection.

In Bertot's 2011 systematic review (previously described), only 1 RCT was identified comparing MWA for hepatic metastases with the criterion standard of surgical resection.\(^4\)

In 2011, Pathak et al conducted a systematic review of ablation techniques for colorectal liver metastases, which included 13 studies on MWA (total N=406 patients) with a minimum of 1-year follow-up.\(^2\) Mean survival rates were 73%, 30%, and 16% and ranged from 40% to 91.4%, 0% to 57%, and 14% to 32% at the 1-, 3-, and 5-year follow-ups, respectively. Minor and major complication rates were considered acceptable, and ranged from 6.7% to 90.5% and 0% to 19% respectively. Local recurrence rates ranged from 2% to 14%.

In the 2009 systematic review by Ong (previously described), local recurrence rates for liver metastases after MWA treatment averaged 15% but varied between 0% and 50% in the 7 studies that addressed liver metastases.\(^7\)

Randomized and Nonrandomized Trials

In 2013, Liu et al reported on liver metastases for 35 patients treated with MWA (62 tumors) and 54 patients treated with RFA (70 tumors).\(^2\) Ablation was complete in 89% (117/132) of tumors and did not differ significantly between tumor types: 86% (56/65) for metastatic colorectal cancer and 91% (61/67) for other metastatic diseases. Tumors 3.0 cm or smaller were completely ablated significantly more often than tumors larger than 3.0 cm (94% vs 67%, p=0.001).

In 2011, Lorentzen et al retrospectively reviewed MWA in 39 patients with 125 liver metastases from the primary sites of colorectal cancer (n=31), breast cancer (n=6), carcinoid tumor (n=1), and gastrointestinal stromal tumor (n=1).\(^2\) Complete ablation was achieved in 100% of tumors (median size, 1.5 cm) with 1 treatment session in 34 patients, in 2 sessions for 4 patients, and in 3 sessions for 1 patient. One case of liver abscess, which resolved after percutaneous drainage, was the only major complication reported. Four minor complications were reported (1 incidence of ascites, 3 complaints of puncture site pain). At median follow-up of 11 months, LTP was seen in 12 (10%) of 125 tumors in 10 (26%) of the 39 patients.

In a prospective, single-institution, phase 2 study, Martin et al (2010) reported on 100 patients treated with 270 open or MWA for HCC (n=17) and liver metastases from the primary sites of colorectal (n=50), carcinoid (n=11), and other cancers (n=22, including cholangiocarcinoma, metastatic breast, renal cell carcinoma, bladder, carcinoid, melanoma, and sarcoma).\(^2\) Median tumor size was 3.0 cm. Thirty-eight patients received MWA, 53 patients had MWA plus concomitant hepatic resection, and 9 patients had MWA concomitant with other organ resection. Only 2 patients had incomplete ablations after the procedure. No bleeding complications were experienced, but 2 cases of hepatic abscess and 2 cases of hepatic insufficiency occurred. At median follow-up of 36 months, 5 patients had incomplete ablations, and 2 (2%) patients had local tumor recurrence; 37 (37%) patients developed recurrence at nonablated sites.

In 2000, Shibata et al reported on 30 patients with hepatic metastases from colorectal cancer randomized without stratification to MWA after laparotomy (n=14) or to hepatectomy (n=16).\(^2\) Of the original 40 patients, 10 patients were excluded because researchers discovered intraoperatively that they did not meet study criteria (they had extensive metastasis or ≥10 tumors). The 2 treatment groups did not differ significantly in age (mean age, 61 years in both groups), number of tumors (mean, 4.1 vs 3.0, respectively), or tumor size (mean, 2.7 cm vs 3.4 cm, respectively). No significant differences were observed in survival (27 months for MWA vs 25 months for hepatectomy) or mean DFS (11.3 months for MWA vs 13.3 months for hepatectomy).
However, intraoperative blood loss was significantly lower, and no blood transfusions were required in the MWA group (6 patients in the hepatectomy group required transfusions). Complications in the MWA group included 1 hepatic abscess and 1 bile duct fistula. In the hepatectomy group, complications were 1 intestinal obstruction, 1 bile duct fistula, and wound infection.

Lung Cancer
In 2015, Acksteiner and Steinke reported a retrospective study that evaluated the safety, effectiveness, and follow-up imaging of MWA in 10 patients (age range, ≥75 years) with early-stage non-small-cell lung cancer (NSCLC). Follow-up with computed tomography and fluorine 18 fluorodeoxyglucose-positron emission tomography (FDG-PET) extended for 30 months (median, 12 months). No peri-procedural deaths or major complications were reported. Seven patients were DFS. Three patients showed growth of the treated lesions, 1 patient died (age 90) due to unknown cause 18 months post-surgery. One patient still living presented with local progression and disseminated metastatic disease at 12 months. One patient showed increasing soft tissue mass at the ablation site 15 months post-treatment, but 3 consecutive core biopsies over 2 months failed to confirm tumor recurrence.

A 2015 observational study evaluated the clinical efficacy and utility of percutaneous MWA therapy for lung cancer without surgical treatment. Thirty-nine lesions in 29 patients with peripheral lung cancer were treated by percutaneous MWA therapy under local anesthesia. Treatments were completed in 29 patients. Average surgical time was 8 minutes (range, 5-12 minutes). Eight, 14, 4, and 3 patients achieved complete remission, partial remission, stable status, and progression, respectively, for an effectiveness rate of 76%. Complications included 5, 2, and 15 cases of pneumothorax, pleural effusion, and fever, respectively. No complications from needle track insertion were observed. Mean progression-free survival was 15 months. One- and 2-year OS rates were 91% and 83%, respectively.

In 2012, Lu et al retrospectively reviewed 69 patients treated with MWA for inoperable lung cancer or metastatic pulmonary metastases. OS rates for patients with pulmonary metastases at 1, 2, and 3 years were 48%, 24%, and 14%, respectively. The recurrence-free survival rates for patients with NSCLC at 1, 2, and 3 years were 73%, 50%, and 27%, respectively. OS rates were 67% at 1, 45% at 2, and 25% at 3 years. Pneumothorax occurred in 25% of patients.

In 2013, Belfiore et al reported on a retrospective review of 56 patients treated with MWA for inoperable lung cancer or metastatic pulmonary metastases. DFS rates were 69% at 1 year, 54% at 2 years, and 49% at 3 years. Pneumothorax was reported in 18 (32%) patients.

In 2011, Vogl et al prospectively assessed 80 patients treated with MWA for inoperable pulmonary metastases. Rates were 91% at 1 year and 75% at 2 years. Pneumothorax occurred in 11 (9%) of 130 MWA sessions, and pulmonary hemorrhage occurred in 8 (6%) of 130 sessions.

Primary Renal Tumors
Systematic Reviews
In a 2014 systematic review and meta-analysis, Katsanos et al compared thermal ablation (MWA and RFA) with surgical nephrectomy for small renal tumors (mean size, 2.5 cm). The analysis included 1 randomized study on MWA (described below) and 5 cohort studies on RFA (total N=587 patients). In the ablation group, complication rates and renal function declined were significantly more than in the nephrectomy group (p=0.04 and p=0.03, respectively). The local recurrence rate was 3.6% in both groups (relative risk, 0.92; 95% CI, 0.4 to 2.14; p=0.79) and DFS up to 5 years did not differ significantly between groups (hazard ratio, 1.04; 95% CI, 0.48 to 2.24; p=0.92).

Martin et al conducted a meta-analysis comparing MWA with cryoablation for small renal tumors in 2013. The analysis included 7 MWA studies (n=164 patients) and 44 cryoablation studies (n=2989 patients). Selected studies were prospective or retrospective, nonrandomized,
noncomparative studies. Mean follow-up duration was shorter for MWA than for cryoablation (17.86 months vs 30.22 months, respectively, p=0.07). While mean tumor size was significantly larger in the MWA studies than in the cryoablation studies (2.58 cm vs 3.13 cm, respectively, p=0.04), LTP (4.07% vs 2.53%, respectively; p=0.46), and progression to metastatic disease (0.8% vs 0%, respectively; p=0.12) did not differ significantly.

Clinical Studies
In 2012, Guan et al reported on a prospective randomized study that compared the use of MWA with partial nephrectomy (the criterion standard of nephron-sparing surgical resection) for solitary renal tumors less than 4 cm.42 Forty-eight patients received MWA and 54 had partial nephrectomy. Patients in the MWA group (6 [23.5%]) had significantly fewer postoperative complications than in the partial nephrectomy group (18 [33.3%]; p=0.019). MWA patients also had significantly less postoperative renal function declines (p<0.009) and estimated perioperative blood loss (p<0.001) than partial nephrectomy patients. At last follow-up, estimated glomemualr filtration rate declines in both groups were similar (p=1.00). Disease-specific deaths did not occur, and overall local recurrence-free survival by Kaplan-Meier estimates at 3 years was 91.3% for MWA and 96.0% for partial nephrectomy (p=0.541). Longer follow-up is needed.

In 2012, Yu et al reported on a retrospective review of 46 patients treated with MWA for renal cell carcinoma.34 Complete ablation occurred in 98% (48/49) of tumors (mean tumor size, 3.0 cm). At a median follow-up of 20.1 months, all 46 patients were metastasis-free. OS rates were 100% at 1 year and 2 years and 97.8% at 3 years.

In 2011, Muto et al reported on complete tumor coagulation necrosis in 10 patients treated with MWA for clear cell renal carcinoma (median tumor size, 2.75 cm).35 Depending on tumor size, the microwave antennas were used 1 to 3 times and mean application time was 14.1 minutes. No complications were reported during or after the procedure. Bai et al (2010) reported complete laparoscopic MWA in 17 of 18 clear cell renal carcinoma tumors (mean tumor size, 2.8 cm).36 In this study, evidence of disease progression was not found at a median follow-up of 20 months, including a patient with incomplete ablation followed for 31 months. Complications reported were mild (18.2%), and renal function did not significantly deteriorate.

In a 2011 study of 10 patients with solid-enhancing renal tumors (median size, 3.65 cm) who were treated with MWA, Castle et al reported tumor recurrence in 3 of 8 tumors at a mean follow-up of 17.9 months.37 Because tumor size was larger in this study, mean ablation time was 21 minutes. Additionally, 20% of patients experienced intraoperative complications while 40% experienced postoperative complications, including perinephric hematoma, splenic capsular tear, pleuritic chest pain, skin burn, fever, hematuria, genitofemoral neuralgia, and urinoma.

In another study, Guan et al (2010) reported on the safety of MWA for renal hamartoma.38 In this case series, 15 of 16 patients had complete tumor ablation. Disease recurrence was not reported at a median follow-up of 16 months.

Other Tumors or Conditions
No RCTs on the use of MWA for other tumors or conditions have been identified. A systematic review of ablation therapies, including MWA, for locally advanced pancreatic cancer was published in 2014.39 Reviewers found limited evidence on the use of MWA for pancreatic cancer. Case studies and retrospective reviews on MWA for adrenal carcinoma,40 metastatic bone tumors,41 intrahepatic primary cholangiocarcinoma,42 benign thyroid tumors,43 and other nononcologic conditions (i.e., bleeding peptic ulcers, esophageal varices, secondary hypersplenism) were identified.

Locoregional Ablative Therapies
There is research available for each of the ablative therapies. However, many of the studies combine multiple ablative procedures or utilize ablative techniques as an adjunct to surgical
Resection or chemotherapy. Studies also include patients with a broad range of tumor size and etiology. As a result, it is sometimes difficult to draw specific conclusions regarding the efficacy of an ablative technique. Careful selection of candidates for each treatment option and expert application of these treatments are required to achieve best outcomes.

**Laser Ablation**

Laser ablation (LA), also known as laser coagulation therapy, laser interstitial tumor therapy (LITT), and laser interstitial photocoagulation, refers to thermal tissue destruction by conversion of absorbed light (usually infrared) into heat.\(^{44,45}\) The infrared energy penetrates tissue directly for a distance of 12 to 15 millimeters (mm) and temperatures above 60 degrees centigrade cause rapid coagulative necrosis and instant cell death. The most widely used device for LA techniques is the Nd: YAG (neodymium: yttrium-aluminum-garnet) laser (Flexilase; Living Technology, Glasgow, Scotland) with a wavelength of 1064 nanometers (nm). Additionally, more compact diode lasers with shorter wavelengths (800 nm to 980 nm) have been utilized.\(^{46}\) A range of imaging modalities have been used to guide percutaneous LA techniques including ultrasound-guided needle placement, and magnetic resonance (MR) with contrast. However, the use of this technique is limited by the amount of local experience and resource/machine availability.

Laser ablation has been primarily studied in the treatment of brain, spine, and prostate tumors, but has been cleared by the U.S. Food and Drug Administration (FDA) for any soft tissue tumor (FDA, 2010). Percutaneous LA has received increasing attention for the treatment of a variety of primary and secondary malignant tumors, including hepatic tumors. However, of all the ablation techniques for hepatic tumors, LA has the least amount of published literature.\(^{47}\) Laser ablation is mainly applied in Europe and the majority of data reported on laser ablative techniques came from Italy, Germany, and the United Kingdom (Gough-Palmer & Gedroyc, 2008).\(^{46}\) The majority of long-term survival data was reported on hepatic metastases and varied in the literature; virtually no data has been published for HCC LA.\(^{48}\)

Five-year survival rates of 26% and median survival rates of 27 to 39 months have been reported.\(^{49,50}\) Pacella and colleagues reported on a series of 148 patients (144 biopsy proven HCC) treated with 239 laser ablative sessions.\(^{51}\) The authors quoted long-term survival rates of 89% at one year, 52% at three years, and 27% at five years and an overall complete lesion ablation rate of 82%. Puls et al reported on 87 consecutive patients with 180 liver metastases from CRC who underwent laser ablation with MR thermometry in 170 sessions.\(^{52}\) Median survival time was 54 months and survival rates were 95.7% at one year, 86.2% at two years, 72.4% at three years, 50.1% at four years, and 33.4% at five years. Although, these results appeared encouraging, direct comparison with other ablative therapies (e.g., RFA) in prospective clinical trials are needed to show definitively which modality is superior.

Selection criteria in these studies varied on the technique used and the facilities available but were in general, similar to other locally ablative techniques such as RFA and MWA. Many of the studies were performed on multiple tumor types, making it difficult to evaluate the efficacy of laser ablation. The range of imaging modalities used at follow-up combined with a variety of definitions of treatment success, made comparison of the data difficult.\(^{46}\)

The NCCN guidelines for HCC do not include or discuss LA as a technique of locoregional ablation.\(^{53}\)

While laser ablation appears safe, evaluation of its effectiveness is limited by lack of good comparative trials and hampered by constantly changing technologies. The clinical efficacy of laser ablation has not been established at this time.\(^{46,47}\) Further data from randomized studies evaluating the impact of LA on survival, quality of life, and cost-effectiveness for both primary and secondary liver tumors is required.

**Unresectable Hepatocellular Carcinoma Tumors in the Transplant Setting**

As noted earlier, liver transplantation is the only curative alternative for unresectable HCC.
Locoregional therapies (e.g., ablation, TACE) have been explored in various settings including as a technique to prevent tumor progression in patients on the liver transplant waiting list, downstaging tumors such that the patient will be considered a better candidate for liver transplantation, and decreasing the incidence of post-transplant recurrence in patients with larger (T3) tumors. All of these indications are in part related to the United Network for Organ Sharing (UNOS) liver allocation policy, which prioritizes patients for receiving donor livers. The UNOS policy recognized pretransplant locoregional therapies including “chemoembolization of lesion, radiofrequency, cryo, or chemical ablation of the lesion,” as a component of patient management during the waiting period.

In 2002, UNOS introduced a new liver allocation system, model for endstage liver disease (referred to as MELD) for adult patients awaiting liver transplant. The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (i.e., international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from 6 (less ill) to 40 (gravely ill). Aside from those in fulminant liver failure, donor livers are prioritized to those with the highest MELD number. This scale accurately predicts the risk of dying from liver disease except for those with HCC, who often have low MELD scores since bilirubin, INR, and creatinine levels are near normal. Therefore, patients with HCC are assigned additional allocation points according to the size and number (T stage) of tumor nodules as follows:

- T1: One nodule, 1.9 cm or smaller
- T2: One nodule between 2.0 to 5.0 cm, or two or three nodules each smaller than 3.0 cm
- T3: One nodule larger than 5.0 cm, or two or three nodules with at least one larger than 3.0 cm

In considering how to allocate the scarce donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. Patients with T1 lesions were considered at low risk of death on the waiting list, while those with T3 lesions are at high risk of post-transplant recurrence, and are generally not considered transplant candidates. Patients with T2 tumors have an increased risk of dying while on the waiting list compared to those with T1 lesions and an acceptable risk of post-transplant tumor recurrence. Therefore, UNOS criteria prioritize T2 HCC by allocating additional point’s equivalent to a MELD score predicting a 15% probability of death within three months. This definition of T2 lesions is often referred to as the “Milan criteria,” in reference to a key study reported by Mazzaferro et al that examined the recurrence rate of HCC according to the size of the initial tumor. Note that liver transplantation for those with T3 HCC is not prohibited, but these patients do not receive any priority on the waiting list. All patients with HCC awaiting transplantation are reassessed at three-month intervals. Those whose tumors have progressed and are no longer T2 tumors will lose the additional allocation points.

Therefore, the UNOS allocation system provides strong incentives to use locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list. Promfet et al report of a national conference on liver allocation in patients with HCC in the U.S. addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early stage HCC on the transplant waiting list in the U.S. At the completion of the meeting, there was a general consensus for the development of a calculated continuous HCC priority score for ranking HCC candidates on the list that would incorporate the calculated MELD score, alpha-fetoprotein, tumor size, and rate of tumor growth and that only candidates with at least stage T2 tumors would receive additional HCC priority points.

**Locoregional Therapies as a Bridge to Transplant**

Several studies have reported dropout rates of wait-listed patients treated with locoregional therapy. However, lacking controlled data, it is difficult to assess contributions of locoregional therapy to time on the waiting list. In addition, in 2002, as discussed above, UNOS revised its liver allocation policy, such that wait times for patients with HCC meeting the “Milan criteria” have now declined.
The majority of the literature has focused either on TACE or a variety of locoregional therapies. Given these limitations, the following case series have been reported:

Graziadei et al reported on 48 patients with HCC awaiting transplantation; all underwent TACE every six to eight weeks until a complete response or a donor organ became available. No patients were removed from the list due to tumor progression and mean waiting time was 178 (+/- 105) days. Maddala et al studied the dropout rates of 54 patients receiving TACE while awaiting transplantation. During a median waiting time of 211 days (range: 28 to 1,099 days), the dropout rate was 15%. Obed et al reported on 20 patients with non-progression of lesions after TACE who had liver transplantation; median survival in this group was 92.3 months.

Fisher et al reported on 33 patients who received multimodality ablation therapy, consisting primarily of RFA or TACE. Five patients (12%) were removed from the waiting list after waiting five to 14 months. In this protocol, patients with tumors larger than 5 cm were not considered transplant candidates until the tumor was completely ablated using TACE, RFA, or another technique. Yamashiki et al reported on 288 patients given various ablative therapies; the dropout rate due to tumor progression at one and three years was 6.25 and 23%, respectively. Tumors larger than 3 cm affected the dropout rate due to tumor progression. Mazzaferro et al reported on 50 patients with HCC who underwent RFA while awaiting transplantation; no patient had to be removed from the waiting list due to tumor progression over a mean wait time of 9.5 months. The median tumor size was 3 cm, and 80% of patients met the Milan criteria. Similarly, Lu et al reported on 52 patients who underwent RFA as a bridge to transplantation, 42 of whom met the Milan criteria. After a mean of 12 months, 5.8% had dropped off the waiting list due to tumor progression.

In a 2008 paper, Belghiti et al reviewed the literature reporting efficacy of local management approaches including resection, TACE, RFA, and no treatment. They concluded RFA can induce complete necrosis in the majority of small tumors (less than 2.5 cm) and there was no data demonstrating that the treatment reduced the rate of dropout before transplantation or improved survival after transplant. None of the studies included data from U.S. centers for patients listed after adoption of the Milan criteria. Poretti et al retrospectively compared 31 patients treated with RFA with 33 untreated controls. Only 20% of treated tumors demonstrated complete ablation (necrosis) as defined by histologic examination of the entire lesion. Only 55% of lesions with histologic viable tumor was detected by MRI after pretransplant therapy. After 36 months of follow-up, there was no difference between the treated and untreated groups in overall survival (84 versus 91%), disease-free survival (74% versus 85%), cancer recurrence (23% versus 12%), or mortality from cancer recurrence (57% versus 25% - all respectively) (p > 0.1). The authors concluded viable tumor frequently persisted after pretransplant locoregional therapy and neoadjuvant treatment did not appear to improve post-transplant outcomes in the current MELD era.

The UNOS policy on allocation of livers indicated candidates whose tumors have been ablated after meeting the criteria for additional MELD/PELD (PELD calculator for persons under age 12 years) points will continue to receive additional points (equivalent to a 10% increase in mortality) every three months without review, even if the estimated size of residual viable tumor falls below stage T2 criteria. The policy also noted candidates may be removed from the listing if they are determined to be unsuitable for transplantation based on progression of HCC.

**Locoregional Therapies to Downstage Hepatocellular Carcinoma Prior to Transplant**

Yao et al analyzed longer-term outcome data on HCC downstaging in a cohort of 61 patients with tumor stage exceeding T2 criteria enrolled between June 2002 and January 2007. Eligibility criteria for downstaging included: 1) one lesion larger than 5 cm and up to 8 cm; 2) two to three lesions with at least one lesion larger than 3 cm and not exceeding 5 cm, with total tumor diameter up to 8 cm; or 3) four to five lesions with none larger than 3 cm, with total tumor diameter up to 8 cm. Transcatheter arterial chemoablation and laparoscopic RFA (LRFA) either
alone or in combination were the main methods used: 11 patients received LRFA alone, 14 received TACE and LRFA, and nine received TACE and percutaneous RFA. A minimum observation period of three months after downstaging was required before liver transplant.

Tumor downstaging was successful in 43 patients (70.5%). Thirty-five patients (57.4%) received liver transplant, including two with live-donor liver transplantation. Treatment failure was observed in 18 patients (29.5%), primarily due to tumor progression. In the explant of 35 patients who underwent transplant, 13 had complete tumor necrosis, 17 met T2 criteria, and five exceeded T2 criteria. The Kaplan-Meier intention-to-treat survival analysis at one and four years after downstaging was 87.5% and 69.3%, respectively. The one-year and four-year post-transplantation survival rates were 96.2% and 92.1%, respectively. No patient had HCC recurrence after a median post-transplantation follow-up of 25 months. The only factor predicting treatment failure was pretreatment alpha-fetoprotein greater than 1,000 ng/mL. From this small series, the authors concluded successful downstaging can be achieved with excellent post-transplant outcomes.

Lewandowski et al compared radioembolization with chemoembolization (TACE) in the efficacy of downstaging 86 patients with HCC from stage T3 to T2. Patients were treated with either 90-yttrium microspheres (n = 43) or TACE (n = 43). Median tumor size was similar between the two treatment groups (5.7 and 5.6 cm, for TACE versus radioembolization, respectively). Partial response rates were 61% versus 37% for radioembolization versus TACE, respectively with downstaging from T3 to T2 in 58% of patients treated with radioembolization versus 31% with TACE (p < 0.05).

As part of a national conference involving transplant physicians, workgroups were formed to discuss the policy of assigning increased priority for candidates with stage T2 HCC on the transplant list in the U.S. The workgroup assigned to the role of downstaging in transplant candidates with HCC noted inconsistent outcomes reported in the literature and proposed a definition of downstaging that would include TACE and various ablative techniques but not resection. Promfret et al noted that only two regions have adopted a downstaging protocol.

The results and efficacy of downstaging with TACE to achieve a reduction in tumor burden to a T2 lesion remain controversial. There are retrospective data showing the ability to downstage patients with TACE, however, there is no randomized evidence that tumor downstaging prior to liver transplant confers a survival advantage.

Locoregional Therapies to Reduce Risk of Recurrence of T3 Tumors
Published literature by Pomfret et al reflects an ongoing discussion as to whether the UNOS allocation criteria should expand to include patients with larger tumors. An additional indication for locoregional therapies focused on their use in patients with T3 tumors, specifically to reduce the incidence of recurrence post-transplant. If the incidence of recurrence can be reduced, then Yao et al, Yao et al, Fernandez et al, Merli et al, and Sauer et al reported that advocates have argued the UNOS allocation criteria should not discriminate against patients with larger tumors. Some patients with T3 lesions apparently are cured with liver transplant, although most experience recurrent tumor. For example, in the seminal 1996 study by Mazzaferro et al, the four-year recurrence-free survival was 92% in those who met the Milan criteria (T2 lesion) compared to 59% in those who did not; Sauer et al reported additional studies confirmed this difference in recurrence-free survival rate. However, other institutions have reported similar outcomes with expanded criteria. For example, Yao and colleagues at University of California at San Francisco (UCSF) reported similar recurrence-free survival after transplant in patients with T2 and a subset of those with T3 tumors. This T3 subset was defined as a single lesion less than 6.5 cm or less than three lesions with none greater than 3 cm and with a sum of tumor diameters less than 8 cm. These expanded criteria are known as the UCSF criteria reported by Yao et al.

The question is whether locoregional therapies (including both RFA and TACE) may decrease the recurrence rate in patients meeting the UCSF criteria. Yao and colleagues published a detailed
analysis of 121 patients with HCC who underwent transplantation. Seventy-eight patients (64%) had T2 lesions, while an additional 27 patients (22.3%) met the expanded UCSF criteria, termed T3A lesions. The rest had T1, T3B, or T4 lesions. Individual patients received a variety of preoperative locoregional therapies, including TACE or ablative therapies, such as PEI, RFA, or combined therapies. A total of 38.7% of patients did not receive preoperative locoregional therapy. The one- and five-year recurrence-free survival was similar in those with T2 and T3A lesions, while the corresponding recurrence-free rates were significantly lower for those with T3B and T4 lesions.

The authors also compared recurrence-free survival of those who did and did not receive locoregional therapy. For those with T2 lesions, the recurrence rates were similar whether or not the patient received locoregional therapy. However, for T3 lesions (including both T3A and T3B), the five-year recurrence-free survival was 85.9% for those who received locoregional therapy compared to 51.4% in those who did not. When the data for T2 and T3 lesions were grouped together, the five-year recurrence-free survival was 93.8% for those who received locoregional therapy compared to 80.6% in those who did not. The authors concluded preoperative locoregional therapy may confer a survival benefit in those with T2 or T3 lesions. The authors noted several limitations to the study, including the retrospective nature of the data and the marginal statistical significance of the improved survival given the small numbers of patients in each subgroup. For example, only 19 patients were in the T3A (i.e., UCSF expanded criteria) subgroup. In addition, no protocol specified which type of locoregional therapy to offer different patients. These therapies are only offered to those patients with adequate liver reserve; such patients may have an improved outcome regardless of the preoperative management.

**Summary of Evidence**
For individuals who have an unresectable primary or metastatic tumor (e.g., breast, hepatic [primary or metastatic], pulmonary, renal) who receive MWA, the evidence includes case series, observational studies, cohort studies, randomized controlled trials, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related mortality and morbidity. Available studies have shown that MWA results in a wide range of complete tissue ablation (50%-100%) depending on tumor size, with complete ablation common and nearing 100% with smaller tumors (e.g., ≤3 cm). Tumor recurrence rates at ablated sites are very low. However, tumor recurrence at nonablated sites is common and may correlate with disease state (e.g., in hepatocellular carcinoma). Intraoperative and postoperative minor and major complications are low, especially when tumors are smaller and accessible. While some earlier studies found MWA required more treatment sessions to achieve adequate ablation, more recent studies using newer MWA technology that deliver larger ablation zones with cooled-shaft antennas have demonstrated shorter ablation times and fewer complications.

In conclusion, although comparisons among the various locoregional therapies are difficult due to factors such as interstudy patient and treatment heterogeneity, differences in patient management protocols and multimodality treatment protocols, the body of data illustrates the likely overall benefit of certain locoregional therapies for specific patient populations.

**Supplemental Information**

**Clinical Input from Physician Specialty Societies and Academic Medical Centers**
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

**2016 Input**
In response to requests from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies and 1 academic medical center in 2016. This number of responses was less than optimal. Input overall was mixed. There was some support for the medical
necessity of microwave ablation (MWA) in each category, with some reviewers indicating that it was standard of care for certain tumors. However, there were no indications for which all 3 reviewers agreed that MWA should be medically necessary.

2011 Input
In response to requests from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies (3 reviews) and 4 academic medical centers (6 reviews). Eight reviewers considered MWA investigational to treat primary tumors such as hepatocellular carcinoma, benign and malignant renal tumors, lung tumors, adrenal tumors, or cholangiocarcinoma. The reviewers noted insufficient evidence and a need for further studies on MWA. However, 1 reviewer indicated MWA for primary tumors, including, but not limited to hepatocellular carcinoma, benign and malignant renal tumors, lung tumors, adrenal tumors, or cholangiocarcinoma, may be considered a treatment option, and another reviewer indicated that MWA for renal tumors may be considered a treatment option.

Four reviewers considered MWA investigational to treat liver metastases. However, 2 reviewers indicated MWA for liver metastases may be considered a treatment option. One reviewer noted MWA may be appropriate for tumors not amenable to radiofrequency ablation or other local treatments. This reviewer also indicated MWA may be more appropriate for tumors located near large blood vessels.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines on hepatobiliary cancers (v.3.2017) lists microwave ablation (MWA) (along with radiofrequency ablation [RFA], cryoablation, and percutaneous alcohol injection) as a treatment option for hepatocellular carcinoma (HCC) tumors in patients who are not candidates for potential curative treatments (e.g., resection and transplantation) and do not have large-volume extrahepatic disease. Ablation should only be considered when tumors are accessible by percutaneous, laparoscopic, or open approaches. The guidelines indicate that HCC tumors of 3 cm or less may be curatively treated with ablation alone. HCC tumors between 3 and 5 cm may also be treated with ablation to prolong survival when used in combination with arterial embolization. Additionally, the tumor location must be accessible to permit ablation of the tumor and tumor margins without ablating major vessels, bile ducts, the diaphragm, or other abdominal organs. However, only 2 reviews were cited in the guideline to support recommendations for ablative techniques, but these reviews are not specific to MWA (category 2A).

The National Comprehensive Cancer Network guidelines for neuroendocrine tumors (v.3.2017) do not mention MWA. Guidelines state that: “Cytoreductive surgery or ablative therapies such as radiofrequency ablation (RFA) or cryoablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B). For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended.”

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence updated its guidance on MWA for treatment of metastases in the liver in 2016, replacing a 2011 guidance. The revised guidance indicated that: “Current evidence on microwave ablation for treating liver metastases raises no major safety concerns and the evidence on efficacy is adequate in terms of tumor ablation.”

The Institute also published guidance on MWA for HCC in 2007. This guidance indicated: “Current evidence on the safety and efficacy of microwave ablation of hepatocellular carcinoma appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.” The guidance also stated there are no major concerns about the efficacy of MWA, but noted that limited, long-term survival data are available.
American College of Chest Physicians
The American College of Chest Physicians’ 2013 evidence-based guidelines on the treatment of non-small-cell lung cancer noted that the role of ablative therapies in the treatment of high-risk patients with stage I non-small-cell lung cancer is evolving.80 RFA, the most studied of the ablative modalities, has been used effectively in medically inoperable patients with small (<3 cm) peripheral non-small-cell lung cancer that are medical stage I.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>NCT01340105</td>
<td>Microwave Versus Radiofrequency Ablation for Hepatocellular Carcinoma: A Prospective Randomized Control Trial</td>
<td>92</td>
<td>Apr 2016 (unknown)</td>
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</table>

NCT: national clinical trial.

References


71. Fernandez JA, Robles R, Marin C et al. Can we expand the indications for liver
transplantation among hepatocellular carcinoma patients with increased tumor size?

**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical, and/or consultation reports and progress notes including:
  - Clinical indications/justification of procedure
  - Eastern Cooperative Oncology Group functional status (if applicable)
  - Previous treatment(s), duration, and response(s)
  - Treatment plan
  - Tumor type and description (i.e., resectable or unresectable, primary or metastatic, tumor burden [e.g., liver dominant])
- Pertinent radiological imaging results (i.e., abdominal CT and/or MRI and/or PET)
- Pathology report including tumor node metastasis (TNM) classification
- Current serum chemistry, liver function tests, and tumor marker results

**Post Service**

- Results/reports of tests performed
- Procedure report(s)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms.
of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<td>60699</td>
<td>Unlisted procedure, endocrine system</td>
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<td>76940</td>
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### ICD-10 Diagnosis

All Diagnoses

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<td>09/30/2015</td>
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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.
Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.